Bandolier 77

What do we think?
What do we know?
What can we prove?

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Paper: towards a new future

Internet may be good, but paper is still king, at least for GPs in the Northern & Yorkshire Region. A recent survey indicated that almost 40% of GPs read it cover to cover every month. But from 2001 the way ***Bandolier*** is funded will change as R&D budgets tighten. There will be continued support for the knowledge production, but not for paper copies in the same way as now.

Bandolier is seeking to forge a stronger partnership with primary care groups, health authorities and trusts. In the next few weeks ***Bandolier*** will be writing to chief executives with preliminary details of a new scheme centred around local distribution. The aim is to minimise costs of production while maintaining that independent look at how to help decision makers find and appraise evidence, and how to put it into practice.

The more organisations participating, and the more copies printed, the lower will be the unit cost of each copy. Just what the costs will be depends on uptake in a direct way. Initial projections are that if half of all PCGs participate, then it will be possible to deliver 100 copies of ***Bandolier*** per month to each PCG for about £500 a year. This is about 40p per copy per month, the price the NHS has paid for the last seven years since ***Bandolier*** began.

We will keep you in touch in later issues as the story unfolds, but in the meantime readers who appreciate ***Bandolier*** might help inform organisations policies.

Internet update

After some months of server confusion ***Bandolier*** on the Internet is delighted to return to its previous hosts in the University of Oxford Medical School. The address below will get you to the revamped site. Previous stories have been aggregated into over 30 topic headings, and there is a superlative new search engine. Make sure that you change your address book, and email a friend with the address.

In this issue

TREATMENT EFFECTIVENESS AND COSTS IN REFLUX DISEASE

Gastro-oesophageal reflux is a common disorder, but only a small proportion of people actually seek help from their doctors. For those who do, there is a bewildering array of possibilities, from advice about lifestyles to endoscopy, depending on age, symptoms, and just where you live. One of the questions ***Bandolier*** is often asked is about the relative efficacy of different treatments, particularly histamine antagonists (H2As) and proton pump inhibitors (PPIs). There is one systematic reviews from McMaster [1], which gives some answers, but the date of the last search was 1996.

Search

MEDLINE and manual journal searches were made for English language studies which were randomised single or double blind studies of treatment for gastro-oesophageal reflux. Patients had to have endoscopic grade II to IV oesophagitis, the endpoint was endoscopic healing, and patients had to be adults. The number of healed patients was extracted for up to 12 weeks of treatment.

Results

The analysis in the paper concentrated on the speed of healing. For this analysis, ***Bandolier*** extracted information at four and eight weeks for any dose of drug where there were at least two studies and at least 100 patients. What this gives us is the proportion of people healed for each treatment at four and eight weeks (Table 1; Figures 1 and 2). Information was also available on complete relief of heartburn at baseline, and after four and eight weeks (Table 2).

What the results of the review show is:

1. Few people get better without treatment. Fewer than 20% are healed with placebo at four weeks, and that increases to about 30% at eight weeks.
2. Higher healing rates are found after eight weeks than after four weeks. Duration of treatment matters.
3. Standard doses of histamine antagonists are much less effective than standard doses of proton pump inhibitors. By eight weeks proton pump inhibitors should heal 82-95%: histamine antagonists might heal 25-58%.
4. Assessment of efficacy by heartburn relief gives similar results to those for endoscopic healing (Table 2).

Symptoms, and especially heartburn, are the critical issue in primary care, and this can be informed by a recent trial

Table 1: Endoscopic healing at 4 and 8 weeks

Endoscopic healing of Grade II-IV oesophagitis with placebo, histamine antagonists and proton pump inhibitors

	4 weeks		8 weeks	
Drug / daily dose	Healed/Total	95% CI of percent healed	Healed/Total	95% CI of percent healed
Placebo	105/629	14 - 20	147/467	27 - 36
Cimetidine 1600 mg	34/147	16 - 30	54/167	25 - 39
Ranitidine 300 mg	258/668	35 - 42	451/831	51 - 58
Ranitidine 600 mg	268/754	32 - 39	422/717	55 - 63
Ranitidine 1200 mg	139/277	44 - 56	184/271	62 - 74
Omeprazole 20 mg	623/1033	57 - 63	171/197	82 - 92
Omeprazole 40 mg	208/320	60 - 70	262/319	78 - 86
Pantoprazole 40 mg	310/422	70 - 78	372/422	85 - 91
Lanzoprazole 30 mg	209/255	77 - 87	231/249	90 - 95

From randomised, blind studies, with at least two studies or 100 patients [from Chiba et al, 1997]

looking at treatment in this setting [2]. This randomised double blind study recruited patients with heartburn in primary care. About half were women, the mean age was about 49 years, the mean weight 77 kg, about 40% had hiatus hernia, about half had endoscopic oesophagitis, symptoms were moderate or severe in about 80% of the patients and about half had symptoms every day.

They were randomised between placebo, omeprazole 20 mg daily or cisapride 40 mg daily. After eight weeks, the number with adequate control of heartburn (one day a week or less with no more than mild heartburn) was much higher for omeprazole than other treatments (Figure 3).

What is interesting is that the patients included were different from those in the systematic review [1], as those all had endoscopically proven oesophagitis. Yet the 76% rate of symptom control for omeprazole was in the middle of the confidence interval for symptom control in the review (Table 2).

Intermittent treatment

A continual complaint is that it's not the healing, but the repeat prescriptions that lead to the huge rise in prescribing costs. Another recent randomised trial [3] shows that only half of patients who have their symptoms healed need ongoing treatment.

Table 2: Symptomatic relief at 4 and 8 weeks

Complete relief of heartburn with placebo, histamine antagonists and proton pump inhibitors

	Baseline		4 weeks		8 weeks	
Drug / daily dose	Heartburn free /Total	95% CI of % heartburn free	Heartburn free /Total	95% CI of % heartburn free	Heartburn free /Total	95% CI of % heartburn free
Ranitidine 300 mg	7/305	1 - 4	120/283	37 - 48		
Omeprazole 20 mg	33/860	3 - 5	621/846	70 - 76	323/416	74 - 82
Omeprazole 40 mg	20/279	4 - 10	220/274	76 - 85	162/188	81 - 91
Pantoprazole 40 mg	5/435	0 - 2	362/413	85 - 91		

From randomised, blind studies, with at least two studies or 100 patients [from Chiba et al, 1997]

Figure 1: Endoscopic healing at 4 weeks. Bars are 95% CI.

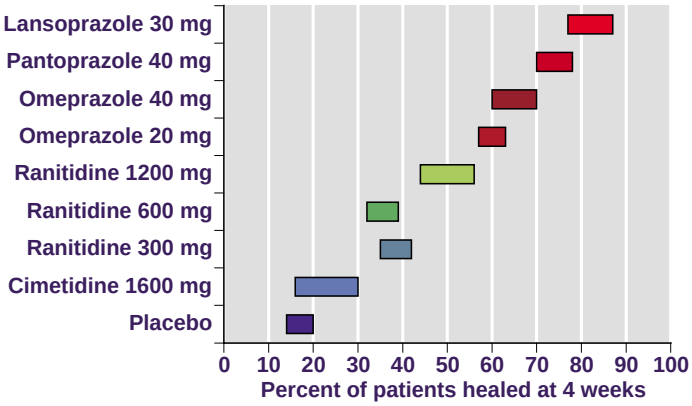


Figure 2: Endoscopic healing at 8 weeks. Bars are 95% CI.

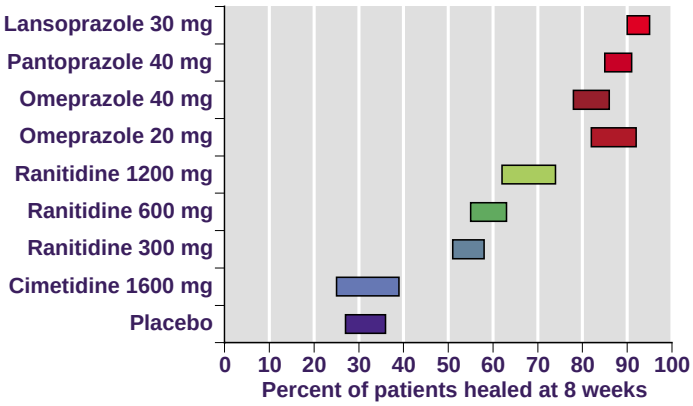
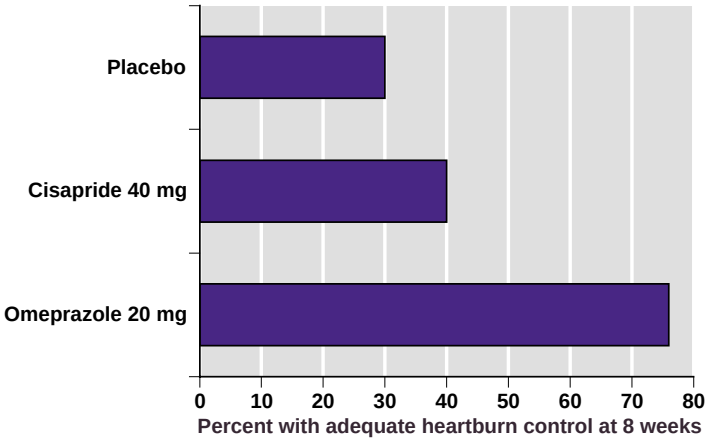


Figure 3: Adequate control of heartburn at 8 weeks



The study recruited patients from primary and secondary care who had moderate or severe heartburn for more than two days in the previous two weeks. About half were women, the mean age was about 48 years, about a quarter smoked, their mean body mass index was 27 kg/sq metre, three quarter had had symptoms for more than 12 months and a third had a normal oesophagus on endoscopy.

They were randomised between ranitidine 300 mg a day, or omeprazole 10 mg or 20 mg. After two weeks patients with no symptoms over the previous week entered a one-year follow up. For those who were not symptom free, doses were increased or continued for a further two weeks. After four weeks all patients, whether healed or with mild symptoms entered the follow up period.

Seventy-two percent of patients had no relapse or only a single relapse needing intermittent treatment over the year. Forty-seven percent reached the end of the study using an intermittent treatment and without recourse to maintenance treatment. The only feature of patients that indicated a shorter time to final treatment failure was smoking.

Costs and budgets

Bandolier has been told that evidence-based medicine plays second fiddle to budget-based medicine, and disaggregated budgets at that. Medicine acquisition costs rule, OK! We don't look at costs in health services as a whole.

With reflux disease the argument seems to be between two different approaches. Step-up treatment involves beginning with lifestyle advice (eating, smoking, drinking), raising the bedhead, and then using alginates, perhaps H2As and then maybe an endoscopy before using a PPI. Step-down treatments involves starting with an effective medicine like a PPI, and when the patient is cured advising about smoking cessation, weight reduction, and reflux control with alginates and H2As from the pharmacist.

A study from 1995 [4] suggests that step up is better, because it assessed costs over six months for initial treatment with cisapride, ranitidine and omeprazole from a computer database. The overall six-month costs were (in 1996 £) £136 for cisapride, £177 for ranitidine and £189 for omeprazole per patient.

This was based on information from only 250 patients. Problems were that it was audit of clinical practice during 1995 rather than what is known to be best practice, that patients with more severe disease were excluded, that patient outcomes are not mentioned, nor the quality of the database. Many other studies conclude that step-down treatment is more cost-effective (and at least it is effective). One such [5] is a cost-effectiveness analysis from the randomised trial [3] comparing initial ranitidine and initial omeprazole. There were no significant savings from initial use of ranitidine, which was significantly less effective [3]. The trouble is that few of these health economic analyses are truly independent, which is a problem.

Bandolier was struck by the representations of Figures 1 and 2. They show not only the expected proportion of patients cured, but also those not cured. Patients who are not cured presumably have other things happen to them - more visits to the GP or outpatients, more drugs, more diagnostics, more endoscopy. That all consumes resources. Perhaps we should think about the balance between the simple costs of treatment, usually the acquisition costs of the medicines, and the consequences of not being cured.

So we assumed that the consequences of not being cured for moderate or severe gastro-oesophageal reflux disease was £100. It could easily be this, given the cost of a GP visit as £16, an outpatient visit at £65, an endoscopy at £200 and a course of drugs from about £20-£70 per month. If you do a few sums, it is clear that PPIs are cheaper than H2As and doing nothing, both in cost per patient healed at eight weeks (Figure 4) and in total cost (Figure 5). A new study from Stamford confirms this view of the world [6] demonstrated for the UK previously [7], and concludes that step down

Figure 4: Cost for each patient healed at 8 weeks

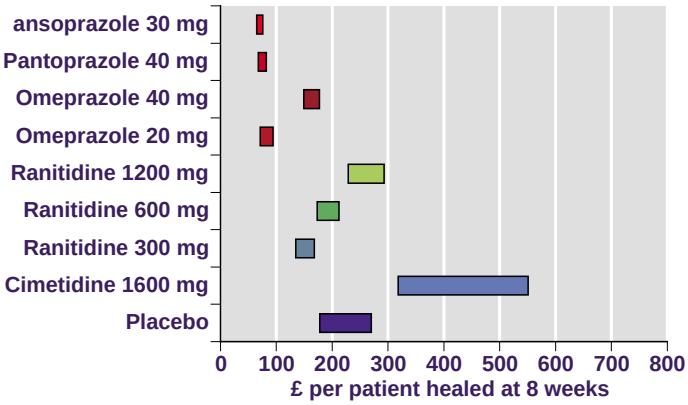
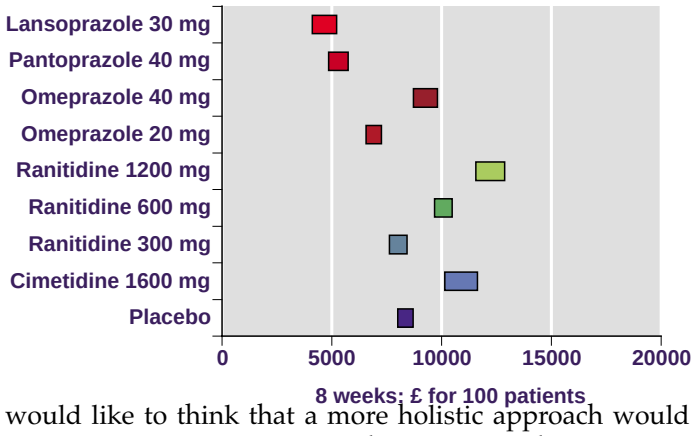


Figure 5: Total cost of treatment



treatments are likely to be the most cost-effective when success rates with PPIs are above 59%, which they clearly are at four or eight weeks (Table 1). Following the evidence could save considerable resources in the NHS (***ImpAct***, July 1999; www.jr2.ox.ac.uk/bandolier/ImpAct/imp02/i2-2.html)

Comment

Bandolier has learned several lessons from this. Firstly that the world does not stand still, and that more good information keeps coming our way. Decisions made today may be right on what we know. The trouble is what we choose to know then becomes rigid while the truth moves on.

Another lesson is to beware stereotypes. We are told that reflux disease is a lifestyle problem brought about by eating curries, drinking lager, smoking and being overweight. Yet in the two randomised trials mentioned above the patients were predominantly in their 40s or older, few smoked, they weren't obese and had suffered for a long time before seeking help. Not exactly typical lager louts.

Perhaps finally it brings home something important. That budget based medicine is not good medicine. If budget based medicine leads to using less effective treatments, then we are in tricky territory. It's all a matter of balance, of course, and for those who have to manage budgets in isolation, life must be difficult. ***Bandolier*** sympathises, and would like to think that a more holistic approach would make it easier for all of us. In the meantime the old adage that the most expensive medicine is the one that doesn't work seems to be provable.

Reference:

1 N Chiba et al. Speed of healing and symptom relief in grade II to IV gastroesophageal reflux disease: a meta-analysis. Gastroenterology 1997 112: 1798-1810.

2 JG Hatlebakk et al. Heartburn treatment in primary care: randomised, double- blind study for 8 weeks. BMJ 1999 319: 550-553.

3 KD Bardhan et al. Symptomatic gastro-oesophageal reflux disease: double blind controlled study of intermittent treatment with omeprazole or ranitidine. BMJ 1999 318: 502-507.

4 A Eggleston et al. Cost effectiveness of treatment for gastro-oesophageal reflux disease in clinical practice: a clinical database analysis. Gut 1998 42: 13-16.

5 NO Stalhammer et a. Cost effectiveness of omeprazole and ranitidine in intermittent treatment of symptomatic gastro-oesophageal reflux disease. Pharmacoeconomics 1999 16: 483-497.

6 LB Gerson et al. A cost-effectiveness analysis of prescribing strategies in the management of gastroesophageal reflux disease. American Journal of Gastroenterology 2000 95: 395-407.

7 C Phillips, A Moore. Trial and error - an expensive luxury: Economic analysis of effectiveness of proton pump inhibitors and histamine antagonists in treating reflux disease. British Journal of Medical Economics 1997 11: 55-63.

LITHIUM AUGMENTATION FOR TREATMENT-RESISTANT DEPRESSION

Antidepressants remain the staple treatment of depression, yet some patients treated with them will fail to make a satisfactory improvement, and some of these may develop chronic depression. The use of lithium as an adjunct therapy has been suggested for about a decade, and a new and interesting meta-analysis [1], with some methodological twists, suggests that the strategy is indeed effective.

Search

Searching was extensive, using MEDLINE, the Cochrane Library, and reference lists of reviews and text books. The object was to identify placebo controlled double blind studies involving patients treated with lithium or placebo after not responding to conventional antidepressants. Trials had to use accepted diagnostic criteria for depression, and the use of acceptable measurements of depression improvement as an outcome measure.

Results

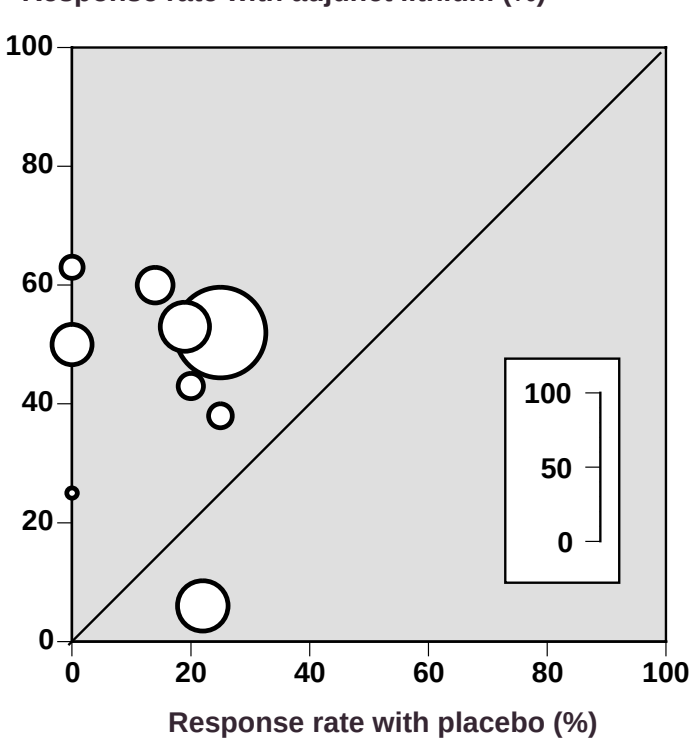
Nine randomised double blind studies were found with 234 patients. Patients included had mean ages from 37 years to 54 years, and were predominantly women. Almost all studies used the Hamilton rating scale for depression (HAM-D), and initial scores ranged from ≥12 to >18, after three to six weeks of treatment with an antidepressant drug. Again, most studies required a reduction in the HAM-D score of 50% or more to define a patient as responding.

Lithium doses ranged from 250 mg a day to 1200 mg a day, with some studies allowing titration to a serum lithium level (usually 0.5 mmol/L or more). Duration of therapy was a little as two days to as long as 42 days.

Table 1: Calculations for highly valid and all trials

Trial type	Number of trials	Improved/Total (%) with Lithium	Improved/Total (%) with Placebo	Relative benefit (95% CI)	NNT (95% CI)
Minimum dose 800 mg/day AND minimum duration 2 weeks	3	27/54 (50)	13/56 (23)	2.2 (1.3 to 3.7)	3.7 (2.3 to 11)
All trials	9	50/113 (45)	21/121 (18)	2.5 (1.6 to 3.8)	3.8 (2.6 to 6.6)

Figure 1: Trials of lithium and placebo in treatment-resistant depression



The results from all the trials were fairly consistent (Figure 1). Three studies (Table 1) which had doses of lithium of at least 800 mg or a dose sufficient to reach serum lithium levels of at least 0.5 mmol/L, and a minimum duration of two weeks had a number needed to treat of 3.7 (95% CI 2.3 to 10.6). For all trials the number needed to treat was 3.8 (2.6 to 6.6).

The authors used cumulative meta-analysis to demonstrate effects of duration of treatment (Figure 2) and dose (Figure 3) on the relative benefit of treatment.

Comment

There are two main points here. First is that despite a relative paucity of data, from only 234 patients, the authors were able to demonstrate a consistent effect and recommend that lithium augmentation of conventional antidepressants should be for at least seven days and at doses sufficient to reach effective levels of lithium.

Second is that seem to have found a neat way to deal with a common problem in meta-analysis, namely that of performing sensitivity analysis with different doses and durations of treatment. This is a technique that could profitably used elsewhere. Often we exclude information if dose is too low (or high) and duration too short. This method allows us to be more inclusive and for decisions on efficacy to be made on more information.

Figure 2: Cumulative meta-analysis according to the duration of lithium augmentation. Bars are 95% confidence interval of relative benefit.

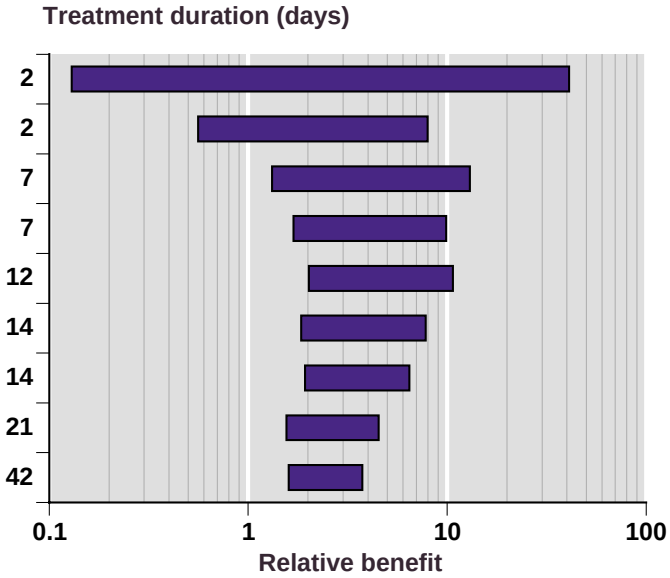
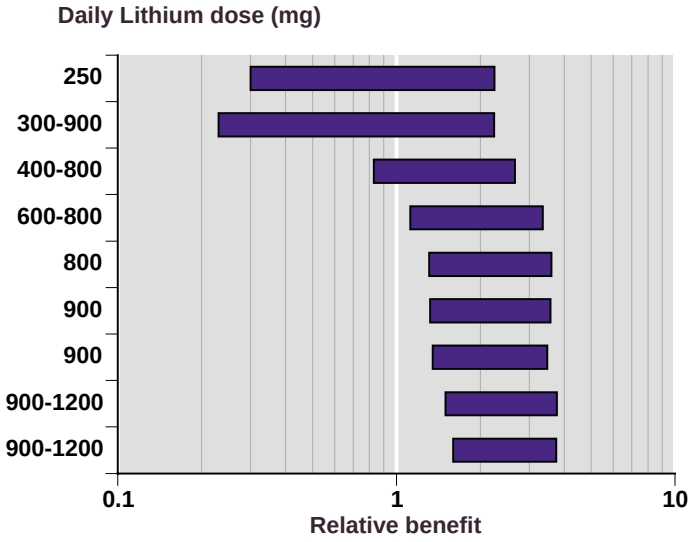


Figure 3: Cumulative meta-analysis according to the dose of lithium. Bars are 95% confidence interval of relative benefit.



Reference:
1 M Bauer, S Döpfmer. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. Journal of Clinical Psychopharmacology 1999 19: 427-434.

REDUCING ANTIBIOTIC PRESCRIBING

Brownie points are seldom available for doing the simple things that make a difference. ***Bandolier*** was taken, therefore, by a study that investigated a method of reducing unnecessary antibiotic prescribing [1] published in a journal with one of the highest impact factors, namely JAMA. It seemed to be just the sort of thing that the new primary care groups in England could be doing to find ways to ensure that best practice becomes the norm.

Study

This was a non-randomised study of four medical office practices in Colorado. Two practices (47,000 people) acted as controls, one (36,000) had a limited intervention, and one (35,000) had a full intervention to try to limit unnecessary antibiotic prescribing. Baseline information as collected over November 96 to February 97, and during the same period the following year when the interventions were applied.

Interventions were based on preliminary studies that identified key factors that had to be addressed in making a change. As usual, this needed a multifactorial approach. The full intervention site received household and office-based patient education materials and a clinician educational intervention. Information was mailed to 25,000 households. It included:

- Refrigerator magnets about self-care, prevention, when to seek care and what to expect from office visits for colds, flu and bronchitis.
- A pamphlet produced by CDC on antibiotics and children.
- A pamphlet addressing proper handwashing techniques.
- A letter from the practice announcing a campaign to combat antibiotic resistance by reducing unnecessary antibiotic use.

In the physicians office there were posters attached to the wall of each room, with information sheets on the limited role of antibiotics in acute bronchitis or chest colds for patients, plus graphics describing the whole problem of antibiotic resistance in Colorado.

There was also a full physician and nurse education programme, including education on evidence-based management of acute bronchitis and how to say no to patient demands for antibiotics. Meetings were led by the medical director who became the programme champion.

The limited intervention site received office-based educational material only. The control sites received no material.

Eligible patients included all adults who made an office visit for acute bronchitis, sinusitis or upper respiratory tract infection during baseline or study period. Information about diagnosis, prescriptions and return visits was obtained from databases.

Results

All four sites had similar rates of visits and prescription of antibiotics during the baseline collection of data. In the following year in the full intervention site the percentage of patients with uncomplicated bronchitis fell from 78% to 44%. There was no change for the limited intervention site or the control sites (Figure). At the full intervention site the number of return visits did not increase, nor was there any increase in the proportion of patients (about 1%) returning with pneumonia. There was no change in prescribing of antibiotics for uncomplicated upper respiratory tract infections (low) or sinusitis (high). The numbers of visits was the same between baseline and intervention periods.

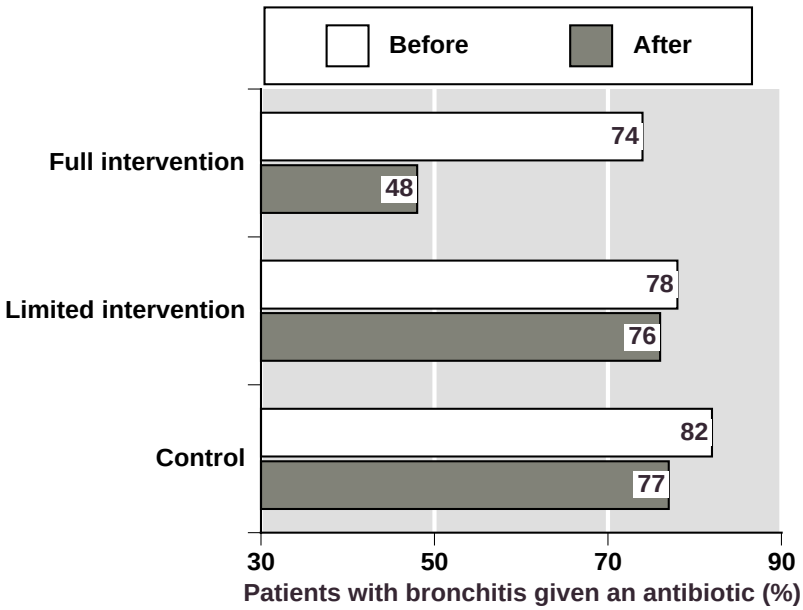
Comment

This wasn't a randomised trial, nor could it be blinded. It was very good, though, because it set out to study a problem, found the levers of change, and pulled them. It involved patients, their professional carers, it informed, and it was based on evidence. And, of course, it worked. No surprise there for anyone who has ever been involved with quality improvement in industry. It uses classic techniques.

It is interesting to think about how expensive this or similar schemes would be to implement in a primary care group. Some organisational costs, some printing costs, some time to obtain and present the evidence well. This paper is worth a read for anyone who wants to make things better.

Reference:
1 R Gonzales et al. Decreasing antibiotic use in ambulatory practice. Impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults. JAMA 1999 281: 1512-1519. Materials on line at (www.uchsc.edu/uh/gim/educate/bronchitis.html)

Figure 1: Reduction in antibiotic prescribing, by intervention



DEFIBRILLATOR USE IN OUT-OF-HOSPITAL CARDIAC ARREST

Cardiac arrest occurring outside hospital will be treated using emergency medical services that might have a range of resources available, including advanced life support systems with cardiopulmonary resuscitation, defibrillation, intubation, artificial ventilation and intravenous administration of medication. A new meta-analysis [1] has explored the literature to see whether any particular technique or combination is better.

Search

The review searched MEDLINE up to mid 1977 for articles in English, and examined bibliographies of papers. It included only published studies that looked at a several different systems (Table 1), and which had data on survival to hospital discharge. This information was extracted, plus response time interval, the proportion of patients to whom bystanders had applied cardiopulmonary resuscitation and the type of system used to treat patients.

Results

Thirty-seven articles had information on over 33,000 people suffering cardiac arrest out of hospital. None of the studies was a randomised study. The analysis investigated the effect of independent variables – the proportion of bystander cardiopulmonary resuscitation, defibrillator response interval and type of system used – on the survival to hospital discharge.

Table 2 shows both the crude survival figures and the odds ratios after making allowance for other variables. Greater survival to hospital discharge was associated with the type of system used, and also with increases in bystander cardiopulmonary resuscitation and reduced defibrillator response time interval.

For bystander cardiopulmonary resuscitation, every 5% increase was associated in an absolute increase in survival of between 0.3% and 1%. A 1 minute decrease in the defibrillator response time was associated with an absolute increase in survival of 0.7% to 2.1%.

Comment

The review perhaps emphasises what we might have guessed. Getting in early with cardiopulmonary resuscitation, defibrillation and pre-hospital advanced life support all contribute to improved chances of survival for someone suffering from cardiac arrest outside hospital. There may be no randomised trials, but this is the best information we have. It is a carefully and cleverly done review that would help anyone responsible for designing or delivering emergency services (though readers in Wales may be distressed to find that it claims south Glamorgan for England!).

Reference:
1 G Nichol et al. A cumulative meta-analysis of the effectiveness of defibrillator-capable emergency medical services for victims of out-of-hospital cardiac arrest. Annals of Emergency Medicine 1999 34: 517-525.

Table 1: Definitions of different systems of life support after cardiac arrest examined in the study

System of support	Definition
Basic life support (BLS)	Administration of oxygen and cardio-pulmonary resuscitation
BLS with defibrillation (BLS-D)	Additional use of automatic or manual defibrillators
Advanced life support (ALS)	Providers trained to perform endotracheal intubation and administer intravenous medications
BLS + ALS	Where basic life support is followed by advanced life support
BLS-D + ALS	Where basic life support with defibrillator is followed by advanced life support

Table 2: Outcomes with different systems of life support after cardiac arrest examined in the study, using both crude survival percentage and odds ratios after allowance for differing rates of bystander cardiopulmonary resuscitation and other confounders

System of support	Survivors / Total	Percent (95% CI)	Odds ratio (95% CI)
BLS-D	815/12433	6.6 (6.1 to 7.0)	1
ALS	560/10072	5.6 (5.1 to 6.0)	1.71 (1.09 to 2.70)
BLS + ALS	842/7502	11.2 (10.5 to 11.9)	1.47 (0.89 to 2.42)
BLS-D + ALS	221/2359	9.4 (8.2 to 10.5)	2.31 (1.47 to 3.62)

Prehospital thrombolysis for MI

The goal of starting thrombolysis early after a heart attack is one known to most people through television medical dramas. Out of the ambulance, into the emergency room, and get some lines up. A new meta-analysis [1] tells us that additional benefit comes from beginning thrombolytic therapy before the patient gets to hospital.

Search

The analysis had an extensive search strategy in a number of electronic databases, and included reviewing any grants that may have been given for this type of research in the USA. Authors and manufacturers were also contacted.

To be included a study had to be a randomised controlled trial of prehospital with in-hospital thrombolysis in acute myocardial infarction. The main outcome was all-cause hospital mortality.

Results

Six studies made it into the final analysis, with 6434 patients. Most did not have concealment of randomisation, and outcomes were not assessed blind. Three different thrombolytic agents (anistereplase, TPA and urokinase) were given in mobile intensive care units (four trials) or by GPs (1) or paramedics (1). Diagnosis of infarction varied between clinical impression and detailed criteria including ECG changes. One large trial had over three-quarters of the patients, and three trials had fewer than 150 patients in total.

Trials reported the time from onset of symptoms to thrombolysis (Figure 1). The time between onset of symptoms and start of thrombolysis was about 60 minutes shorter when thrombolysis was started before hospital admission. Over all, 324 of 3167 patients (10.2%) died in hospital when thrombolysis was begun in hospital. When thrombolysis was begun before hospital admission 280 of 3257 patients (8.6%) of patients died in hospital (Figure 2). This meant that for every 61 patients who had thrombolysis begun before hospital admission, one fewer would die than if thrombolysis had begun in hospital. The NNT was 61 (95% CI 33 to 488).

Figure 1: Mean time between symptoms and start of thrombolysis

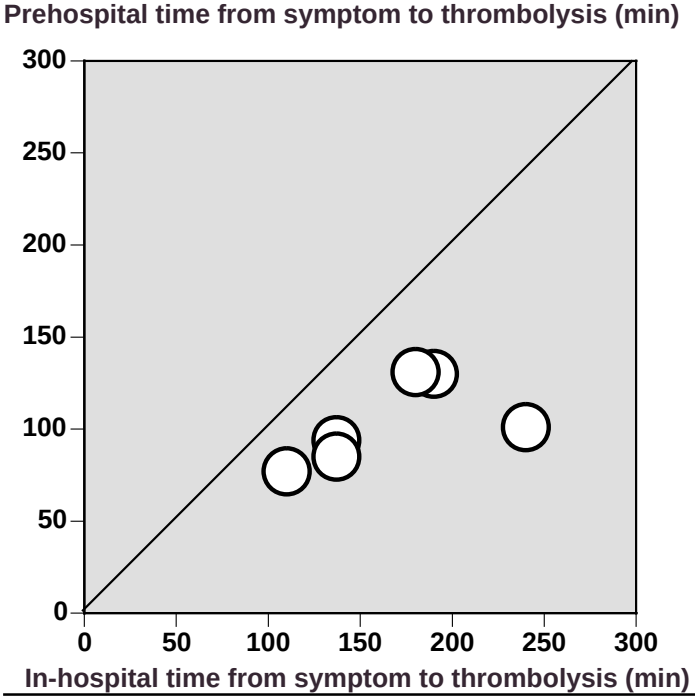
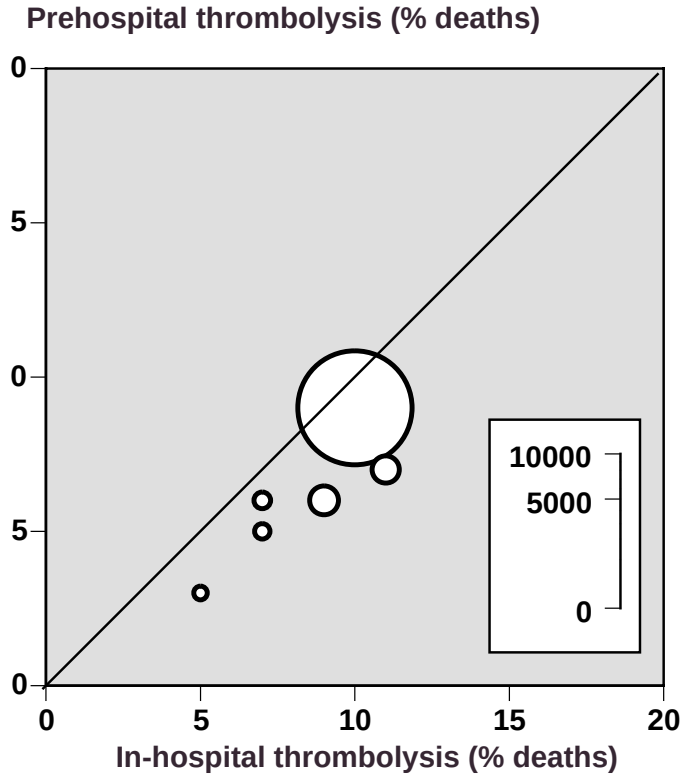


Figure 2: Percentage of patients dying in hospital



Sensitivity analysis showed that results were similar irrespective of trial quality or provider of thrombolysis.

Comment

As we have come to expect from the folks at McMaster, this is a splendid review performed to high standards, and it shows a small but significant benefit from starting thrombolysis before patients get to hospital. This is likely to be particularly beneficial in circumstances outside cities, where the delay before admission to hospital may be delayed because of distance or circumstance.

Reference:
1 LJ Morrison et al. Mortality and prehospital thrombolysis for acute myocardial infarction. JAMA 2000 283: 2686-2692.

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